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Zusatzpatent zum Hauptpatent Nr. 357403

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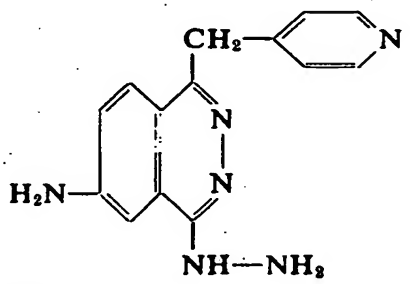
Verfahren zur Herstellung neuer Phthalazine

Dr. Jean Druey, Riehen, und Dr. Adrian Marxer, Muttenz, sind als Erfinder genannt worden

Gegenstand der Erfindung ist ein Verfahren zur Herstellung von 1-Hydrazino-4-(pyridyl-methyl)-phthalazinen, die im Benzolkern eine Aminogruppe tragen und gegebenenfalls noch weitere Substituenten aufweisen, ihrer Salze und quaternären Ammoniumverbindungen, vorzugsweise von Bz-Amino-1-hydrazino-4-[pyridyl-(2')- oder -pyridyl-(4')-methyl]-phthalazinen.

Als weitere Substituenten, insbesondere am Benzolkern, kommen z. B. Nitro-, Alkyl-, wie Methyl-, oder Alkoxy-, wie Methoxygruppen oder Halogenatome, z. B. Chlor oder Brom in Frage.

Die neuen Phthalazine besitzen wertvolle pharmakologische Eigenschaften. Sie zeigen eine ausgeprägte hypotensive Wirkung und können dementsprechend als blutdrucksenkende Mittel therapeutische Verwendung finden. Besonders hervorzuheben ist in dieser Hinsicht das 1-Hydrazino-4-[pyridyl-(4')-methyl]-7-amino-phthalazin der Formel



und seine Salze.

Das erfindungsgemäße Verfahren ist dadurch gekennzeichnet, daß man ein 1-X-4-(Pyridyl-methyl)-Bz-acylamino-phthalazin, das gegebenenfalls noch weitere Substituenten aufweist und worin X einen austauschfähigen Rest bedeutet und Acyl eine Acylgruppe, vor allem die Acetylgruppe bedeutet, oder eine quaternäre Ammoniumverbindung davon mit Hydrazin umsetzt und die Acylaminogruppe hydrolysiert. X kann z. B. eine freie oder verätherte Mercaptogruppe, z. B. eine Alkylmercaptogruppe, eine reaktionsfähig veresterte oder verätherte Oxygruppe, z. B. ein Halogenatom, vorzugsweise Chlor, oder eine Phenoxygruppe, oder eine Aminogruppe, z. B. eine unsubstituierte oder mono- oder disubstituierte Aminogruppe, wie eine Alkyl- oder Alkylenaminogruppe sein. Die Hydrolyse wird in üblicher Weise, vorteilhaft mittels Säuren durchgeführt.

Bei dem erfindungsgemäßen Verfahren können die Ausgangsstoffe auch unter den Reaktionsbedingungen entstehen. So kann man 1-Amino-3-(pyridyl-methyl)-6-acylamino-isoindolenine mit Hydrazin umsetzen, wobei intermediär 1-Amino-4-(pyridyl-methyl)-6-acylamino-phthalazine entstehen.

Die genannten Reaktionen können in An- oder Abwesenheit von Verdünnungsmitteln, allenfalls auch in Gegenwart von Kondensationsmitteln durchgeführt werden, wobei man außerdem in Gegenwart von Katalysatoren, wie Kupferpulver arbeiten kann. Das als Ausgangsstoff verwendete Pyridyl-methyl-phthalazin kann auch in Form seiner quaternären Ammoniumverbindungen, insbesondere der Niederalkylammoniumverbindungen vorliegen.

Je nach der Arbeitsweise erhält man die neuen Hydrazinverbindungen in Form der freien Basen oder ihrer Salze. Aus diesen können in üblicher Weise die freien Basen gewonnen werden. Von letzteren lassen sich durch Umsetzung mit Säuren, die zur Bildung therapeutisch verwendbarer Salze geeignet sind, Salze gewinnen, wie z. B. der Halogenwasserstoffsäuren, Schwefelsäure, Salpetersäure, Phosphorsäure, Rhodanwasserstoffsäure, Essigsäure, Propionsäure, Oxalsäure, Malonsäure, Bernsteinsäure, Zitronensäure, Weinsäure, Äpfelsäure, Methansulfonsäure, Äthansulfonsäure, Oxyäthansulfonsäure, Benzol- oder To-

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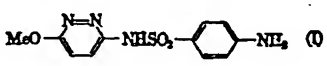
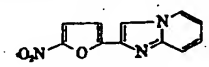
ml. 0.1*N* NaOH overnight at 0° to yield, on acidification with AcOH and crystn. from H_2O at pH 5, 1.2 g. *N*-[*p*-[*β*-(2-amino-4-hydroxy-6(or 7)-pteridinyl)ethyl]benzoyl]glutamic acid, m. 300–10° (decompn.). H. El Khadem

3-Methoxy-6-(*p*-aminobenzenesulfonamido)pyridazine. Spofa, Sdruzeni Podniku pro Dravotnickou Vyrobu (by Alois Novacek, Bohumir Vondracek, Miroslav Ulrich, Stanislav Kokes, Frantisek Stejskal, and Frantisek Sinkule). Fr. 1,315,022, Jan. 18, 1963; Czech. Appl. Dec. 24, 1959; 5 pp. A soln. of 6.5 g. 3-chloro-6-aminopyridazine and 11.7 g. *p*-acetamidobenzenesulfonyl chloride in 200 ml. pyridine is heated at 60–80° for 2 hrs. The mixt. is neutralized to pH 7 with dil. Na_2CO_3 and evapd. under vacuum at a max. temp. of 80°. The residue is treated with 1 g. Na in 90 ml MeOH in an autoclave at 130° for 12 hrs. The product obtained by neutralization to pH 7 with HOAc followed by evapn. is dissolved in 80 ml. H_2O, adjusted to pH 8.5 with NH_4OH, warmed to 60°, treated with C, filtered, and reprecipitated at pH 5.0 with aq. HOAc (1:1). Washing with H_2O and drying gives 8.55 g. (61%) of 3-methoxy-6-(*p*-aminobenzenesulfonamido)pyridazine (I), m. 182°. R. E. Boucher



(I)

2-(5-Nitrofuryl)imidazo[1,2-*a*]pyridine and 2-(5-nitrofuryl)imidazo[1,2-*a*]pyrimidine. Norwich Pharmacal Co. (by Peter H. L. Wei). Belg. 623,469, Jan. 31, 1963; U.S. Appl. Oct. 11, 1961; 5 pp. 2-(5-Nitrofuryl) halomethyl ketones are treated with 2-aminopyridine (Ia), and 2-aminopyrimidine, in $HCONMe_2$ to give the title compds. which can be used as bactericides. Thus, a soln. of 82 g. 2-(5-nitrofuryl)bromomethyl ketone in 70 ml. $HCONMe_2$ is added to a soln. of 66 g. Ia in 300 ml. EtOH, the mixt. heated until the formation of solid material and cooled,



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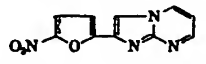
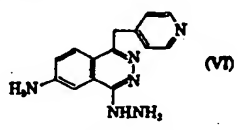


(II)

and the solid filtered off and washed with EtOH and ether to give 51 g. 2-(5-nitrofuryl)imidazo[1,2-*a*]pyridine (I), m. 252–4° ($MeNO_2$). Similarly prepd. is 2-[2-(5-nitrofuryl)]imidazo-[1,2-*a*]pyrimidine (II), m. >300° (decompn.) ($HCONMe_2$). MDPF

***N*-Carbamoyloxyalkyl barbiturates.** Philippe Gold-Aubert (to Sapos S.A.). U.S. 3,075,983 (Cl. 260–256.4), Jan. 29, 1963; Brit. Appl. Nov. 23, 1959; 6 pp. The title compds. have been prepd. by heating the Na salt of a barbiturate with a halohydrin deriv. Thus, 25.4 g. phenobarbitone sodium is heated with 11 g. glycerin chlorohydrin in 100 cc. EtOH for 4–6 hr., NaCl formed is filtered off, and the filtrate evapd. to dryness. The residue distd. at 200°/0.05 mm. and the distillate crystd. affords 5-phenyl-5-ethyl-3-(2,3-dihydroxypropyl)barbituric acid, m. 98°; dicarbamate m. 80°. Similarly, the following 5-phenyl-5-ethyl-3-(2-hydroxy-3-substituted-propyl)barbituric acids were prepd. (substituent given): ethoxy, propoxy, isopropoxy, butoxy, propargyloxy, benzoyloxy, and phenoxy. These compds. possess high therapeutic values as sedative and soporific drugs. V. P. Arya

Phthalazines. CIBA Ltd. (by Jean Druey and Adrian Marxer). Swiss 361,812 (Cl. 12*p*), June 30, 1962, Appl. Mar. 7, 1958; 2 pp. Addn. to Swiss 357,403 (See Ger. 1,061,788, *CA* 55, 13458*c*). 4-Nitrophthalic acid anhydride and 4-methylpyridine in 1,2-$Cl_2C_6H_4$ is treated at 180° to give 5-nitro-3-(4-pyridylmethyl)phthalone (I). I on refluxing for 3 hrs. with 4 times its amount of $NH_2NH_2.H_2O$ gives 1-oxo-4-(4-pyridylmethyl)-7-amino-1,2-dihydrophthalazine (II), m. 298° (HCl salt m. >300°). II refluxed with 6 times its amt. of Ac_2O for 3 hrs., cooled, filtered, and the ppt. in AcOH treated with 2.4*N* alc. HCl gives the 7-acetamido analog (III). III (16.5 g.) is heated for 3 hrs. with 100 cc. $POCl_3$ on a water bath, the suspension added to 600 g. ice, this soln. added slowly to 310 cc. concd.

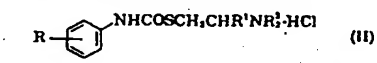


(VI)

NH_4OH, filtered, and washed with H_2O to give 1-chloro-4-(4-pyridylmethyl)-7-acetamidophthalazine (IV). IV is refluxed 2 hrs. with 81 cc. $NH_2NH_2.H_2O$ in 90 cc. MeOH, evapd. at reduced pressure, 200 cc. EtOH added and evapd., and this process repeated to give a residue, which is dissolved in MeOH, filtered, and the filtrate evapd. to give 1-hydrazino-4-(4-pyridylmethyl)-7-acetamidophthalazine (V), m. 143–5°, resolidifies at 180° and then does not melt below 315°; di-HCl salt m. 264–7° (hygroscopic). V refluxed 1.5 hrs. with 50 cc. concd. HCl gives 1-hydrazino-4-(4-pyridylmethyl)-7-aminophthalazine (VI) tri-HCl salt, m. 285°. VI.3HCl loses 1 HCl on drying or recrystg. VI is used therapeutically to lower blood pressure. C. M. Langkammerer

Tris[*β*-theophyllin-7-ylethyl] phosphate. Rene J. P. Hazard, Jean M. Cheymol, Pierre Chabrier, Avigeel Carayon-Gentil, and Marcelle J. Beauvallet. Ger. 1,146,495 (Cl. 12*p*), Apr. 4, 1963; Fr. Appl. Apr. 14, 1959; 2 pp. $POCl_3$ (6.7 g.) in 15 cc. C_5H_5N was added at 50° to 30 g. 7-*β*-hydroxyethyltheophylline in 90 cc. C_5H_5N. The mixt. was held 8 hrs. at 50° and C_5H_5N distd. The residue in MeOH was chilled to deposit the title compd., $(ThCH_2CH_2O)_3PO$ (I) (Th = theophyllin-7-yl), m. 170°, yield 60%. I has an antispasmodic and cardiovascular effect more intense than theophylline. L. M. Werbel

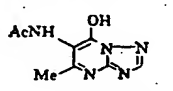
Phenylthiocarbamic acid *S*-esters. Farbenfabriken Bayer A.-G. (by Klaus H. Kisse and Gert Haberland). Brit. 920,755, Mar. 13, 1963; Ger. Appl. Apr. 7, 1960; 6 pp. The basically substituted title compds. are antiinflammatory agents. PhNCO (32 g.) was refluxed with 35 g. $Et_2N(CH_2)_2SH$ in 300 cc. PhMe for 5 hrs., the mixt. filtered after cooling, the filtrate washed with H_2O and evapd., and the residue dissolved in Et_2O and treated with HCl to ppt. 48 g. $PhNHCOS(CH_2)_2NEt_2$ (I).HCl, m. 166°. Similarly were prepd. the following II (R, R^1, NR_2^2, and m.p. given): 3-Cl, H, NEt_2, 155°; H, Me, 4-methyl-1-piperazinyl, 231°; 4-OEt, Me, 4-methyl-1-piperazinyl, 242°; 3-Cl, Me, 4-methyl-1-piperazinyl, 210° (base m. 98°); 4-OEt, H, NEt_2, 152° (methiodide m. 172°); 4-NO_2, H, NEt_2, 248° (decompn.); 2-Cl, Me, 4-methyl-1-piperazinyl, 223°; 4,3-Me(O_2N), Me, 4-methyl-1-piperazinyl, 215°; 4-NO_2, Me, 4-methyl-1-piperazinyl, 216°; 3-Me, Me, 4-methyl-1-piperazinyl, 195°; 2,5-Cl_2, Me,



(II)

4-methyl-1-piperazinyl, 208°; 2,4-Cl_2, Me, 4-methyl-1-piperazinyl, 204°; 3-CN, Me, 4-methyl-1-piperazinyl, — (base m. 100°); 3-CN, H, NEt_2, 170°. I, $b_{0.4}$ 135°, was also prepd. by treating $Et_2N(CH_2)_2SH$ with $COCl_2$ and then with $PhNH_2$. Chizuko Yanaihara

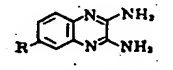
***s*-Triazolo[2,3-*a*]pyrimidine derivatives.** Shionogi & Co., Ltd. (by Yasuo Makisumi). Japan. 7984('62); July 11, Appl. Nov. 26, 1959; 2 pp. A mixt. of 3.3 g. Et *α*-acetamidoacetoacetate and 1.5 g. 5-amino-*s*-triazole is refluxed in 20 cc. AcOH for 3 hrs., evapd., to the residue is added small amt. of EtOH,



(I)

and sepd. mass recrystd. from EtOH to give 1.6 g. 5-methyl-6-acetamido-7-hydroxy-*s*-triazolo[2,3-*a*]pyrimidine (I), needles, m. 292° (decompn.). Heating of I with 10% HCl for 30 min. gives 5-methyl-6-amino-7-hydroxy-*s*-triazolo[2,3-*a*]pyrimidine, needles, m. 281° (decompn.). Similarly prepd. are: 5,7-dihydroxy-6-acetamido-*s*-triazolo[2,3-*a*]pyrimidine (flakes, m. 276–7°), 5,7-dihydroxy-6-amino-*s*-triazolo[2,3-*a*]pyrimidine (needles, m. 282° (decompn.)), 5-hydroxy-6-acetamido-7-amino-*s*-triazolo[2,3-*a*]pyrimidine (flakes, m. >310°), and 5-hydroxy-6,7-diamino-*s*-triazolo[2,3-*a*]pyrimidine (pale yellow needles, m. >300°). These are useful as anti-cancer drugs. Hiroshi Kataoka

2,3-Diaminoquinoxalines. Badische Anilin- & Soda-Fabrik A.-G. (by Hans Weidinger, Joachim Kranz, and Hans G. Haese). Belg. 619,356, Dec. 27, 1962; Ger. Appl. June 29, 1961; 12 pp. 1,2-Diaminobenzenes are treated with compds. of the general formula RO(HN:)CC(:NH)OR, where R is an alkyl group, to give the title compds. which can be used in the prepn. of dyes. Thus, 6 parts 10% HCl is added to a soln. of 30 parts 1,2-$C_6H_4(NH_2)_2$ and 34 parts MeO(HN:)CC(:NH)OMe in 200–50 parts H_2O in 30 min. at room temp., the temp. rises



(I)

to approx. 45° and a ppt. forms, the mixt. is cooled, and the ppt. is filtered off to give 38.4 parts 2,3-diaminoquinoxaline (I, R = H). Similarly prepd. are I (R and m.p. given): Cl, 282°; Me, 246–8°; O_2N, —; MeO, 242°. MDPF

5-Aminomethylpyrimidines. Cilag-Chemie Ltd. (by Ernst Habicht). Swiss 361,573 (Cl. 12*p*), June 15, 1962, Appl. July 12, 1957; 2 pp. 2-(3-Diethylaminopropylamino)-4-amino-5-cyanopyrimidine in 300 cc. MeOH satd. with NH_3 is treated with H at 80–5° in the presence of Raney Ni. The mixt. is filtered, the residue evapd. *in vacuo*, dissolved in 2*N* HCl, the soln. treated with $(NH_4)_2S$ soln. to remove Ni complexes, decolorized with C, and evapd. *in vacuo*. The residue is recrystd. repeatedly from EtOH–EtOAc to give 40–50% of the